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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/693,980

10/28/2003

Thomas P. Jerussi

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01/22/2008

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EXAMINER

POLANSKY, GREGG

ART UNIT

PAPER NUMBER

1611

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/693,980	Applicant(s) JERUSSI, THOMAS P.	
	Examiner Gregg Polansky	Art Unit 1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 41 and 43-49 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 41 and 43-49 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Claims

1. Applicant's Request for Continued Examination (RCE) filed 10/31/2007 is acknowledged and accepted.
2. Applicant's amendments, filed 10/31/2007, canceling Claims 42 and 51 and amending Claim 41, are acknowledged.
3. Claims 41 and 43-49 are pending and presently under consideration.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

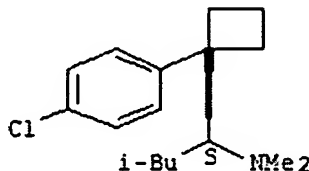
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 41 and 43-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Young, J.W. (WO 94/00114).

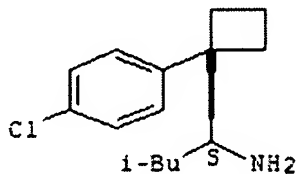
Young teaches the administration of the optically pure (-) isomer (the (S) isomer) of sibutramine to treat depression. See page 29, claim 1. Further, Young teaches the importance of stereochemical purity in the field of pharmaceuticals where chirality is demonstrated. Some stereoisomers are safe and effective while others are teratogenic. *In re Adamson et al.*, (CCPA 1960) 275 F2d 952, 125 USPQ 233. Young teaches the desirability of using the optically pure (-) isomer of sibutramine to avoid the adverse

effects associated with the administration of the racemic form of the compound. See Abstract.

The chemical structure of (S)-sibutramine is:



The demethylation of (S)-sibutramine will result in the (S)/(-) isomer of the resulting desmethylbutramine and didesmethylsibutramine. One of ordinary skill in the art would have easily recognized this. For instance, the chemical structure of (S)-didesmethylsibutramine is:



It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact

inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) (“[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention”). In the instant invention, the Applicant must show that the teachings of the above cited reference (i.e., treatment of depression with (S)-sibutramine) does not work through the instantly claimed method of treating depression with (S)-didesmethylsibutramine.

Luscombe et al. (Neuropharmacology, Vol. 28(2)) is provided for evidentiary purposes to demonstrate that didesmethylsibutramine is one of two active metabolites of sibutramine. See page 129, Summary, and Figure 1 (BTS 54 505 is didesmethylsibutramine).

Young teaches a dose range of (S)-sibutramine of 1 mg to 60 mg per day, starting at a dose of about 5 mg to 15 mg per day, and the dose will vary with the severity of the condition and the route of administration. See page 19, lines 1-21. Young teaches suitable routes of administration include, oral, rectal, parenteral, transdermal, or subcutaneous. See page 21, lines 7-14.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 41 and 43-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young, J.W. (WO 94/00114), in view of Luscombe et al. (Neuropharmacology, Vol. 28(2)).

The teachings of Young are presented *supra*.

Luscombe et al. teach metabolites of sibutramine (which is a tertiary amine), the secondary amine metabolite (BTS 54 354) and the primary amine metabolite (BTS 54 505), which is didesmethylsibutramine, to be of equal efficacy *in vivo* and considerably more active than sibutramine, *in vitro*. See page 129, Figure 1; page 131, Table 1; and

page 132, last paragraph. A dosage range of 0.1-3.0 mg/kg is disclosed on page 130 under *Prevention of reserpine-induced ptosis in rats*.

The references fail to teach optically pure enantiomers of didesmethylsibutramine. However, as discussed *supra*, one of skill in the art would recognize that the (S) isomer of sibutramine (taught by Young), when metabolized *in vivo* (i.e., demethylated), will form the (S) isomer form of the demethylated metabolites (e.g., (S)-didesmethylsibutramine). Thus, administering (S)-sibutramine would inherently yield (S)-didesmethylsibutramine. This knowledge, in addition the combined teachings of Young and Luscombe et al., would have motivated one skilled in the art of formulation chemistry to prepare and administer the (S) isomer of didesmethylsibutramine with a reasonable expectation of success in treating depression. Such would have been obvious in the absence of evidence to the contrary because Young teaches antidepressant activity following the administration of optically pure (S)-sibutramine. Luscombe teaches the close structural relationship of sibutramine and its metabolite didesmethylsibutramine, as well as the demonstration of antidepressant activity of the active metabolite of sibutramine, didesmethylsibutramine. Because didesmethylsibutramine is also optically active, one skilled in the art would have been motivated to resolve the S(-) enantiomer through no more than routine experimentation and compare their efficacy in treating depression to the racemic didesmethylsibutramine. One would have been further motivated to use the (S) isomer in view of Young's teaching of decreased side effects of S-sibutramine compared to the racemic mixture, and the knowledge that (S)-sibutramine is metabolized to the (S)

isomer of the demethylated sibutramine products (e.g., didesmethylsibutramine). It would have been reasonable to expect such S(-) enantiomers would exhibit a lower side effect profile or a faster onset of action.

As required by instant claims 43-45, the determination of both optimal dosage ranges and optimal modes of administration are parameters well within the purview of those skilled in the art through no more than routine experimentation.

With respect to claimed dosage ranges of the active agents in the instant methods, it is not inventive to discover the optimum or workable ranges by routine experimentation when general conditions of a claim are disclosed in the prior art. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233,235 (CCPA 1955) and MPEP 2144.05(11). The determination of the optimum dosage regimen to employ with the presently claimed active agents would have been a matter well within the purview of one of ordinary skill in the art. Such determination would have been made in accordance with a variety of factors. These would have included such factors as the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered a part of a drug combination. Thus, in the absence of evidence to the contrary, the currently claimed specific dosage amounts and dosage regimens are not seen to be inconsistent with the dosages that would have been determined by the skilled artisan.

The additional administration of drugs, as required by claims 48 and 49, such as selective serotonin reuptake inhibitors, serotonin modulators, hypnotics, sedatives, CNS stimulants, are well established in the prior art for the treatment of depression.

Response to Arguments

9. Applicant's arguments, filed 10/31/2007, in response to the Office Action mailed 4/19/2007, have been fully considered but they are not deemed to be persuasive.

Applicant argues that "while [the] Young references may well disclose the 'distinction and advantages' of isomers of sibutramine, they still do not teach or suggest anything regarding the isomers of didesmethylsibutramine". The Examiner disagrees. Distinct optical isomers of sibutramine will maintain their distinct optical rotation when metabolized via demethylation (*supra*). Therefore, the teachings of Young do suggest benefits of administering optically pure isomers, since optically pure forms of sibutramine exert their physiological effects, at least in part, by their correspondingly optically pure metabolites.

Applicant further argues that the Luscombe reference "does not disclose that didesmethylsibutramine is more active as an antidepressant than sibutramine". While the Examiner agrees that Luscombe teaches equivalent therapeutic activity *in vivo* between sibutramine and its demethylated metabolites, the *in vitro* data presented demonstrate a substantial increase in activity by the metabolites. Although *in vivo* activity would have been accorded more weight by those skilled in the art, as suggested by Applicant, the substantially higher *in vitro* activity, in light of the teachings of Young

and the knowledge that sibutramine metabolites maintain optical purity, would have motivated said artisan to evaluate (S)-didesmethylsibutramine activity *in vivo*.

Conclusion

10. Claims 1-17 are rejected.
11. No claims are allowed.
12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571) 272-9070. The examiner can normally be reached on Mon-Thur 8:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Page 10

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Gregg Polansky

A handwritten signature in black ink, appearing to read "Phyllis Spivack". The signature is written in a cursive style with a large "P" and "S".

1/17/08

PHYLLIS SPIVACK
PRIMARY EXAMINER